EXPERIMENTAL STUDIES ON THE COOLING IRRIGATION OF CEREBRAL VENTRICULAR SYSTEM (II)

by

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INTRODUCTION

Many experimental studies have been done on the disturbance of consciousness by means of the various methods as well as clinical investigations. Principally, electrical stimulation have been usually employed as well as the destruction with medicaments or toxic agents against certain localized cerebral areas in the previous experiments. However, concerning the neurological features of hypothermia as a blocking mechanism against the central nervous system few informations are available. The cooling irrigation of cerebral ventricular system from the lateral ventricle, through the third ventricle, aqueduct of Sylvius and fourth ventricle to the major cisterna with cold Ringer's solution on dogs has been previously reported by the present author with successful results of the reversible unresponsiveness to external stimuli.[13]

In the first report, behavioral and physiological changes occured during and after the cooling ventricular irrigation were described. On the other hand, control experiments with use of warm and hot Ringer's solution were also presented from which no unresponsiveness as like as the cooling irrigation was resulted. Therefore it was concluded that the unresponsiveness resulted from this experiment might be ascribed to the effect of hypothermia, and neither to the elevated intraventricular pressure and mechanical impulse to the ventricular wall, nor to the physiological action of electrolytes in Ringer's solution.

The accurate detection of cooling process of the brain matter in this experiments was performed by means of the electrical measurement of temperature in various areas of the brain, and the clarification of localization participating in the unresponsiveness being resulted from this experiment was also performed by several localized cooling irrigations.

METHOD

Adult mongrel dogs weighing 4 to 15 kg in body weight were used. Procedure and conditions of the cooling ventricular irrigation were same as those described in the first report.[13]

For the measurement of cerebral temperature, the micropyrometer with five copper-constantan thermocouples was used. Two of the thermocouples were inserted into the thalamus and the hypothalamus through a burr hole in the parietal skull of opposite side of intubation, while another two were kept towards rostral direction from the cerebellar vermis and the rest one kept in the major cisterna for the measurement of temperature of outflowed fluid throughout the irrigation.

The whole brain was removed immediately after the completion of exeperiment and fixed for about one month in 10 per cent formalin solution. Then the sites of tips of the thermocouples were respectively confirmed macro- and microscopically upon each frontal section of the fixed brain.

The localized cooling irrigations of the ventricular system were performed by following four routes under the identical conditions of which were made on usual ventricular irrigation with cold RINGER's solution: (1) On five dogs the irrigations were done through the way from the lateral ventricle on one side to the other opposite one conducting the ventricular intubation as previously noted. (2) On three dogs the irrigations were performed through the way from the rostral part of third ventricle to the major cisterna after the following operative procedure. Rostral part of the frontal lobes and the bulbi olfactorii were exposed by destruction of the bony walls of the frontal sinus and orbitae, and the superior and inferior sagital sinus were ligated under the opening of the dura mater. The falx of dura was cut off, and the fissure between both hemisphares was dug by small spatulae until the rostral part of the third ventricle through the frontal end of the corpus callosum. Then through this spatium NELATON's catheter of No. 4 to 6 was inserted into the third ventricle. On the other hand, the major cisterna was exposed and opened by the way of separation of the raphe nuchae. (3) On one dogs the irrigation was also done from the caudal pard of third ventricle to the major cisterna. The procedure of intubation into the third ventricle was similar as mentioned above. (4) On eight dogs the irrigation of fourth ventricle was performed through double tube (NELATON's catheter of No. 5 to 7 in which cavity was inserted a vinyl tube about 2mm of diameter), which was inserted into the fourth ventricle via the major cisterna under lifting the cerebellar vermis.

Immediately after the completion of experiment the brain was irrigated with diluted methylen blue solution under the same conditions of irrigation as main experiment. The internal wall of the ventricles was thus stained according to each localized irrigating course. Certification of the irrigated area was made by the estimation of staining upon midline section of the brain after removal of it.

The criteria of unresponsiveness was estimated by the abolishment of the nose pinching response and other facial reflexes which represented an escape reflex against the stimulation from outside as described in the previous paper.

RESULTS

(1) DISTRIBUTION OF THE CEREBRAL TEMPERATURE DURING THE COOLING VENTRICULAR IRRIGATION

Mesurements of temperature were made by means of puncture with thermocouple from the surface of cerebellar vermis towards rostroventral direction, followed by the gradually progressive insertion of it with a rate of one to two mm per 15 sec. during the cooling ventricular irrigation, for the purpose of detection on the

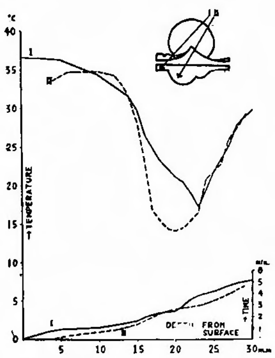

Fig. 1

Upper two curves demonstrate the local temperature at points of various deapth in the caudal brain throughout cooling ventricular irrigation (D 30).

Measurements performed by the meaning of direct insertion with a thermocouple from the vermis of cerebellum to rostroventral, with a rate of about 1mm. per 15 sec.

Curves show a V or U form, and their bottoms agree with the periods at which the thermocouple passing through the cerebrospinal space.

Under two curves demonstrate the deapth of thermocouple in the caudal brain at each period of time, as is noted diagramatically in the right top corner.

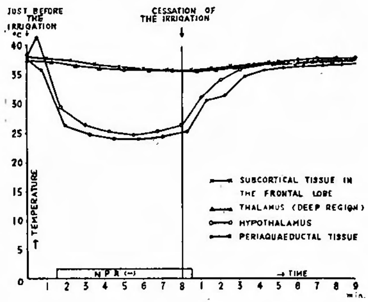

Fig. 2

Alterations of cerebral temperature on various regions in the brain(D 101; irrigated from the left lateral ventricle to the major cisterna with 8°C RINGER's solution at 30cc per min. of flow speed. NPR was abolished from 90 seconds after the beginning of irrigation and reappeared from 30 seconds after the cessation of it. Apnoea and other incident never happened.)

Figure shows steep fall of temperature in the hypothalamus and the periaqueductal tissue and relatively plane curve in the subcortical tissue and deep part of the thalamus.

difference of reduction in temperature in the brain matter on account of the distance from the ventricular wall. One of the results of the mesurements above mentioned is demonstrated as U- or V-formed curves in Fig. 1. In this curves it is verified that the nearer is the brain matter from the cerebrospinal space, the greater is the reduction in temperature.

One of the gradients on temperature in the subcortical tissue, the internal area of the thalamus, hypothalamus and periaqueductal tissue during and after the cooling ventricular irrigation was shown in Fig. 2. In the areas being near from the ventricular wall such as the hypothalamus and periaqueductal tissue the temperature of the brain matter was steeply reduced at initial stage of the irrigation, and later gradually, while in the areas being remote from the ventricular wall such as the subcortical and intrathalamic tissue the temperature was scarcely reduced even during the cooling irrigation. After the cessation of irrigation, temperature of the brain matter was elevated first rapidly later slowly, and reached to the normal level 5 to 10 minutes after the

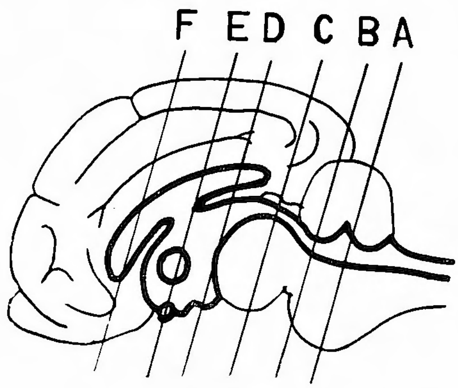

Fig. 3

Levels of frontal section of dog's brain corresponding to each diagrams in Fig. 1.

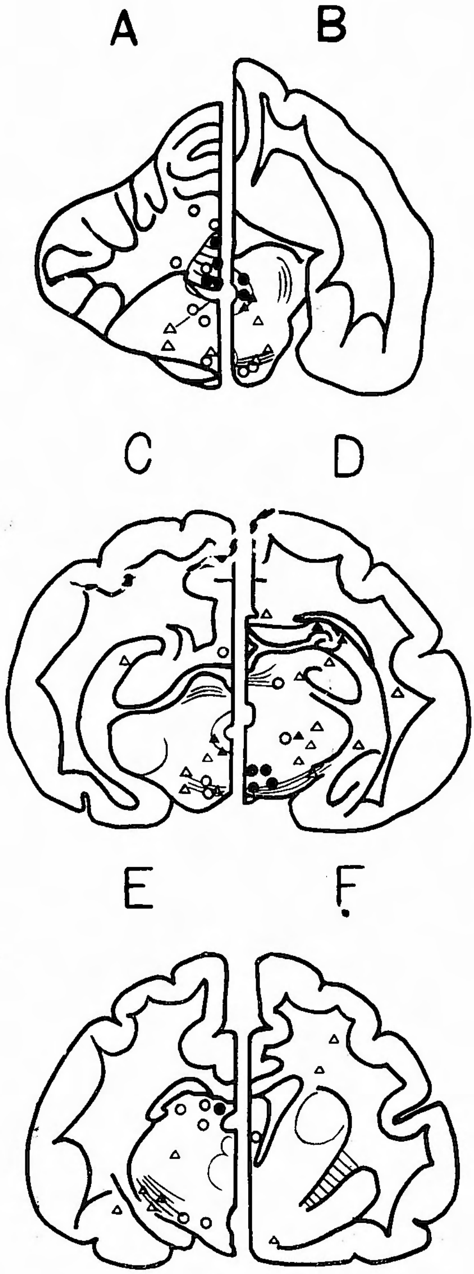

Fig. 4

Diagrams on the frontal sections of dog's brain. (Sectioned level is showen in Fig. 3). Each sections indicate the points inserted the thermocouples. Indications as followed: Open triangles; Fall of temperature at the range of 0–4°C from the beginning of irrigation.
Open circles; that of 4.1∼8°C.
Solid triangles;that of 8.1∼12°C.
Solid circles; that of more than 12°C.

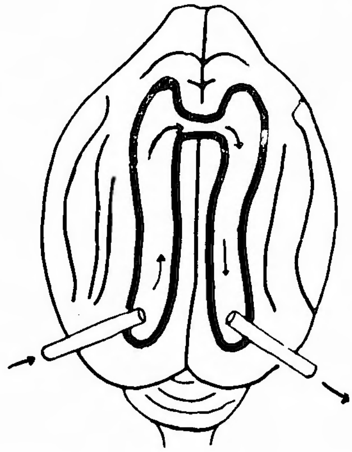

Fig. 5

Diagram of localized cooling ventricular irrigation from the lateral ventricle on one side to the other one, through the foramen of MONRO.

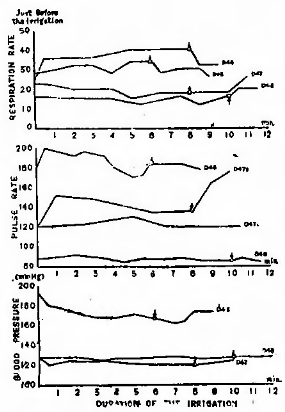

Fig. 6

Traces in the respiration rate, pulse rate and blood pressure during the cooling irrigation from the lateral ventricle of one side to the other one with RINGER's solution. The circles with arrows indicate the stopping points of the irrigation.

cessation.

On twenty dogs the reduction curves of temperature were traced in various areas of the brain by the same method as mentioned above. Then the distribution of reduction rate in temperature at the lapse of one minute after the abolishment of nose pinching response

Table 1. Conditions and results of the cooling irrigation from the

Dog No.	Sex	Body Weight (kg)	Conditions of Irrigation				Changes	
			Speed of Flow (cc/min.)	Duration (min.)	Temp. of Inflowed Fluid (℃)	Temp. of Outflowed Fluid (℃)	Nose Pinching Resp.	Blinking Reflex
45	♂	8	10	6	8	18	Weakened	Unchanged
46	♂	10	24	8	8.5	19	Unchanged	Unchanged
48	♂	15	20	8	9	20.5	Unchanged	Weakened
〃	〃	〃	16	8	12	24	Weakened	Unchanged
49	♂	8	14	10	9.5	20	Weakened	Unchanged

on each curves was plotted in comparison with that before the irrigation upon several frontal sectioned surfaces as shown in Fig. 3 and 4. Consequently, the reduction rates of temperature in the cerebellar vermis, periaqueductal grey matter, hypothalamus and the areas being close to the ventricular wall were larger than the others.

(2) COOLING IRRIGATIONS OF VARIOUS PARTS IN THE CEREBRAL VENTRICULAR SYSTEM

a) Cooling irrigation between both lateral ventricles (Fig. 5).

On five dogs cold RINGER's solution was irrigated from the lateral ventricle on one side to the other one. Consequently, abolishment was not observed in the nose pinching response, corneal and light reflex of pupils with exception of two cases in which resulted the weakening of blinking reflex during the cooling irrigation. On each two cases in this series pupils rendered

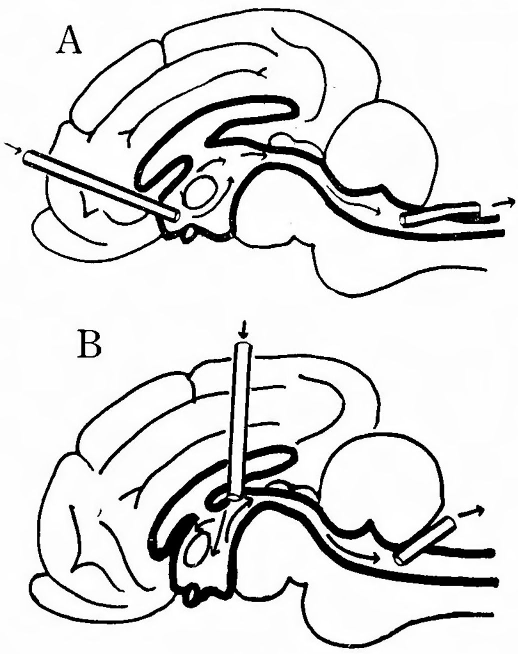

Fig. 7
Diagrams of localized cooling ventricular irrigation from the third ventricle, through the apueduct of SYLVIUS and the fourth ventricle to the major cisterna.
Inflow tube is inserted into anterior (A) or posterior (B) part of the third ventricle.

Table 2. Results of the localized cooling ventricular irrigation from the third ventricle, through the aqueduct of SYLVIUS and the fourth ventricle.

Course of irrigation	Dog No.	Nose Pinching Response
Anterior part of third ventricle → major cisterna	95	disappeared
	100	disappeared
	103	disappeared
Posterior part of third ventricle → major cisterna	90	disappeared

lateral ventricle of one side to the other one with RINGER's solution.

during Irrigation							
Corneal Reflex	Size of Pupils	Light Reflex	Respiration Rate	Pulse Rate	Blood Pressure	Muscle Tonus	Incidents
Unchanged	Reduced	Unchanged	Unchanged	Increased	Lowered	Unchanged	
Unchanged	Reduced	Unchanged	Increased	Unchanged	–	Unchanged	
Unchanged	Enlarged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	
Unchanged	Enlarged	Uuchanged	Decrased	Increased	–	Unchanged	
Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged	

myotic and mydriatic respectively, and the other one unchanged. No significant change in the rates of respiration and pulse and blood pressure was also observed (Table 1 & Fig. 6).

b) *Cooling irrigation from the rostral part of third ventricle to the major cisterna through the aqueduct of Sylvius and fourth ventricle* (Fig. 7A).

All of three cases were irrigated with cold RINGER's solution through such approach as mentioned above, dogs were rendered to be unresponsive from the earlier stage of irrigation (Table 2), while the partial invasion of dye into the lateral ventricles through the foramen of MONRO was recognized in the control irrigation with dye solution

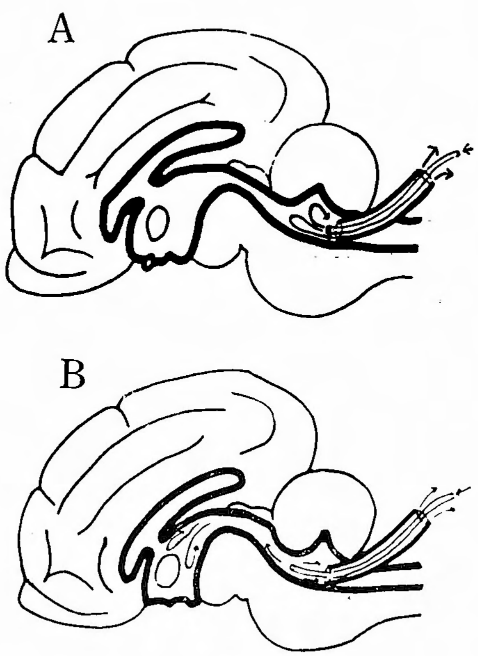

Fig. 8

Diagrams of localized cooling ventricular irrigation from the major cisterna with double tube. (Inflow from internal fine tube and outflow from external thick tube.)

A; irrigated only the fourth ventricle involving caudal part of the apueduct of SYLVIUS.

B; the third ventricle and all extent of the aqueduct of SYLVIUS is also irrigated as simultaneously as the fourth ventricle.

Table 3. Results of the localized cooling ventricular irrigation in the fourth ventricle from the major cisterna with double tube, with or without involving the third ventricle and the aqueduct of SYLVIUS.

Course of irrigation	Dog No.	Nose Pinching Response
Only fourth ventricle without involving third ventricle and aqueduct of SYLVIUS	86 88 102 106	unchanged unchanged unchanged weakened
Fourth ventricle with involving third ventricle and aqueduct of SYLVIUS	91 98 105	disappeared disappeared disappeared

immediately after the cooling irrigation.

c) Cooling irrigation from the caudal part of third ventricle to the major cisterna through the aqueduct of Sylvius and fourth ventricle (Fig. 7B).

In only one case on which such irrigating mechanism as mentioned above could be established the result of effective unresponsiveness was recognized by the irrigation with cold RINGER's solution (Table 2), in spite ot the difficulty of operative procedure because of the fact that the lateral ventricle was apter to be opened than the third ventricle in the median aproach of corpus callosum. In this case it was confirmed that the lateral ventricles were put out from the course of irrigation in the control irrigation with dye solution.

d) Cooling irrigation in the fourth ventricle by means of the insertion of double tube from the major cisterna.

Eight dogs were irrigated with such approach as mentioned above. Five of them in which the irrigated region was limitted within only the fourth ventricle and the caudal end of aqueduct of SYLVIUS (Fig. 8A), were not rendered to be unresponsive with exception of a case in which the nose pinching response was merely weakened. Three of them, which were irrigated more extensively, i. e. the aqueduct of SYLVIUS and the third ventricle were involved due to the excessive high pressure of the irrigating fluid or to the excessively deep insertion of inflow tube (Fig. 8B), were rendered to be completely unresponsive. The irrigated area was also verified with dye (Table 3).

DISCUSSION

From the results obtained from the measurement of cerebral temperature in this experiments, it was confirmed that the slight reduction of temperature was shown in the cerebral cortex and the subcortical tissue during the cooling ventricular irrigation, while many investigators had demonstrated that the brain was the most conductible upon the thermal change than any other tissues.[21 22 43]

On the contrary, remarkable reduction of temperature was observed in the areas being close to the ventricular wall when the unresponsiveness was obtained.

These observations sustain a surmise that the acquired unresponsiveness may be participated in the neural mechanism of the periventricular tissue. In fact, in the brain tissue perfusing constantly with warm blood flow the effect of hypothermia which invades in a limitted area of the brain will not be considered to reach to the remote areas within such short time.

INOUE observed in his study on the cerebral temperature that when a part of cerebral tissue was affected by sudden thermal change, the transient reverse influence of temperature took place in the deep cerebral tissue. From this observation he concluded that the brain would perform certain thermal regulation to preserve its constant temperature against the thermal change from its circumstance.[22]

In the present experiment, likewise, initial transient elevations of temperature were recognized within hypothalamic region on several cases. Regarding this phenomenon, it is a interesting fact that the regulating center of body temperature is localized in the hypothalamus.

In addition, the influence of thiopental sodium on the brain temperature should be considered inasmuch as this experiments being performed under the remaining effect of this anesthetics even though its slight grade. However, this factor may be negligible because of such evidence reported by Inoue and Maeno that the reduction of cerebral temperature under intravenous anesthesia had been recovered before all reflexes came back.[23]

From the detailed data of cerebral temperature in agreement with a previous conclusion, the acquired unresponsiveness in the present experiments may be considered to be ascribed in merely the effect of hypothermia among several factors.

Concerning the relation between cerebral temperature and respiration, Tada reported some decisive observations in his study on the temperature of the brain in freezing course [46]. In his study, even when the cortical temperature fell to 25°C the reduction of respiration was not so remarkable. On the contrary, from our present data, it was ascertained that when the temperature in the periventricular region fell beneath 25° C, respiration rate reduced remarkably and respiratory arrest was apt to occur in spite of slight reduction of cortical or subcortical temperature. Therefore it may be assumed that the periventricular tissue, as the medulla involves the respiratery center, suffered an intense effect of hypothermia, neverthless its influence to the cortex is slight.

In addition, according to the fact that in this experiment the unresponsiveness forewent constantly to the change of respiration, anoxia or brain anemia may be not considered to be responsible for such alteration of responsiveness. Likewise, Lougheed concluded that no anoxia took place in the cerebral tissue under general hypothermia from his experimental results in which no alteration on the lactate-pyruvate ratio in cerebral blood under such condition.[28]

Then, what effect will sustain the brain by hypothermia? This problem have been resolved by Lougheed and Rosomoff in their precise studies.[28, 29, 38~40] They concluded, in short, that under hypothermia the brain metabolism was reduced conspicuously in all phases : cerebral blood flow, cerebral oxygen consumption, cerebrospinal fluid-pressure and brain volume etc.

On the other hand, under the localized hypothermia, like as the present experiment, the reduction of brain metabolism will take place at least in the periventricular tissue, showing remarkable fall of temperature practically under such condition.

In view of the function in the nervous tissue, it is well known since former times that the conductivity of peripheral nerves is reduced when it is encountered to cold [8] Chatfield reported an incompetency on the conduction of stimulus at beneath 9° C in the peripheral nerve [7] On the cranial nerve, likewise, Noell and Brill's observations on the optic nerve showed the reduction of conductivity running parallel with the fall of temperature.[3] This reduction was noted in an arc involving several synapses with as same grade as single nerve fiber by them.

On the central nervous system it has been confirmed by several investigators that the hypothermia effected to lower the conductivity of stimulus [6, 23, 36, 40]. According to these investigations, the fall of cerebral temperature resulted the gradual reduction of electrical activity of the brain, and the spontaneous electrical activity diminished at between 17° C and 21° C of cerebral temperature. Furthermore, FAY and SMITH described in their clinical report concerning general hypothermia that all reflexes gradually weakened as the advance of hypothermia, and disappeared at beneath 25° C of body temperature, then the patient lost a faculty of speaking and became to be "cold anesthetized" in this stage [10].

In general hypothermia the fall of cortical temperature had been considered to contribute such interception on the central nervous system as mentioned above, while in the present experiment the subject of hypothermia has been concerned within the periventricular tissue without the fall of temperature in the cortex. Therefore it will be permitted to consider that the interception is performed within a certain portion as far as where an impulse reaches to cortex in the present experiment, if the depressed wakefulness and sleeping state is elucidated by "deafferentation" of the cortex as KLEITMAN and GAMILLE [21] and BREMER [5] have described.

The experimental results of the localized cooling irrigation by the way of several different irrigating course conduct such possible conclusion that the lateral and fourth ventricle may have no significant relation on the mechanism concerning with the acquired unresponsiveness. Accordingly, the critical area participating in this unresponsiveness may be narrowed in the limitted extent about the ventricular wall involved the third ventricle and aqueduct of SYLVIUS, and in this latter area there exist many important nuclei and ascending tracts by which consciousness or awaked state has been considered to maintain, viz. medial thalamus, hypothalamus and periaqueductal grey matter etc.

As regards the medial thalamus, first, the intralaminar thalamic nuclei and the centre median, which are generally believed as the relay nuclei in the diffuse thalamic projecting system, form the internal wall of the third ventricle, or lay in the position not far from its wall.

MORISON and DEMPSY [32] DROOGLEVER FORTUYN and STEPHENS [9] and HUNTER and JASPER [19] concluded that the highest center which contributes the maintenance of wakefulness existed in these medial thalamic nuclei from their experiments in which electrical stimuli against these nuclei was able to evoke the diffuse electrical activity upon the cerebral cortex.

Especially the centre median, acording to Mc LARDY, [31] was referred as the center propagating an impulse into the thalamus diffusely. Morever, MAGOUN and his coworkers also took notice of these nuclei together to the hypothalamus as an ascending relay between the diffuse thalamic projection system to the cortex, and the reticular activating system in the medial brain stem which contributes to the regulation of sleep and wakefulness by means of the collateral transmission of afferent stimuli from the long sensory nerve [11~15,27,30,33,41,44]. In addition, there is the massa intermedia being considered as the center of sleep by HESS and others [17] in the third ventricle.

Then, in the hypothalamus many investigators have also believed the existence of the center of wakefulness. RANSON observed the somnolence caused by hypothalamic lesion.[37] INGRAM declared also same conclusion from his observation that the destruction of the hypothalamus resulted in a sleep and high voltage slow wave in EEG.[20] Such as a considerable theory was supported by LINDSLEY and others, that the consciousness might be maintained by means of the discharging of the hypothalamic activity to the cortex [27] Likewise, MURPHY and GELHORN suggested that the cortex was activated by the upward hypothalamo-cortical discharge in the waking state.[34] And then, BERNHAUT et al. described of EEG at the arousing response following afferent stimuli that an excitating change appeared not in only the cerebral cortex but in also the hypothalamus.[4]

From these observations it is clearly recognizable that the hypothalamus also plays an important role in the maintenance of wakefulness, while the fact that the conducting tracts from the hypothalamus to the medial thalamic nuclei passing through the periventricular tissue as the observation of KUHLENBECK [25] should be worthy of note.

Finally, periaqueductal grey matter in the brain stem has been also considered to be indispensable area for the maintainance of consciousness by BAILEY and DAVIS[3] [16] and von ECONOMO [47]. ARAKI, likewise, came to a similar conclusion on the basis of the studies on the coma puncture by TAKETOMO and TODA [1,2] and the experiments on the nicotine injection into this critical area by YABUNO [48].

In a word, it may be concluded that the periventricular tissue within a limit of the third ventricle and the aqueduct of SYLVIUS plays an important role for the maintenance of consciousness or wakefulness, for the reason that this area consists of the medial thalamus, hypothalamus, periaqueductal gray matter etc. and periventricular tissue connecting these structures. Therefore, it is possible to conclude that the mechanism of the alteration of responsiveness in the present experiment may be depended on the interception of neural function in this critical area, while more detailed detection of the action point should be technically difficult in the present stage of this experiment.

The essential point in this experiment is the initiation of the unresponsiveness having prompt reversivility, while many interesting problems remain to be studied on the mechanism of this aquired unresponsiveness.

SUMMARY

From the detailed measurement of cerebral temperature during the cooling irrigation of ventricular system it was verified that the fall of temperature of the brain matter was remarkable in the thin layer under the internal wall of irrigated ventricular system, especially in the hypothalamus and circumference of the aqueduct of SYLVIUS, while in the cortical and subcortical tissue the temperature remained to be almost equal to the body temperature.

Moreover, on the base of the results from the localized cooling irrigation by the way of several different courses, the lateral and fourth ventricles may be negligible from the concerns with the occurrence of unresponsiveness in this experiment.

From our experimental observations it was confirmed that dogs became unresponsive to external stimuli only by the cooling of thin layer under the internal wall of the third ventricle and aqueduct of Sylvius.

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和文抄録

脳室灌流冷却に関する研究 第2篇

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前編に引続き，脳室灌流冷却時の脳内各部の温度を測定し，更にこの実験によつて起る意識障碍の作用点を追求するために，2～3の方法により限局的脳室灌流冷却を行つて，次の様な成績を得た．

即ち，灌流冷却中の脳内温度は脳室壁に近い部分程急激な低下を示し，殊に視床下部，中脳水道周辺部組織，小脳虫部等に於てその低下度は著るしいが，皮質下部や視床深部の様に脳室壁から隔つた部分では温度低下は極めて小であつた。

限局的灌流冷却は次の各方法で行つた。(1)両側々脳室間灌流冷却：この場合には刺戦に対する反応を消失する事はなかつた．(2)第3脳室前部或は後部より中脳水道を経て大槽に至る灌流冷却：全例刺戦に対する反応を消失させることが出来た．(3)大槽から第4脳室に2重管を挿入し，主として第4脳室のみを灌流冷却した場合：この場合には灌流範囲が第4脳室から中脳水道の後部に止まる場合には刺戦に対する反応を消失させる事は出来なかつたが，液圧を高めて，灌流液が中脳水道を超えて第3脳室をも冷却する様にすると，反応を完全に消失させ得る事を認めた。

以上の実験成績から，この実験によつて起る意識障碍は，第3脳室及び中脳水道の脳室壁に近接する神経組織の冷却による遮断がその本態であろうと推察し得る。

この事は，この領域が視床内側部，視床下部，中脳水道周囲灰白質等を包括するので，これらの部分に意識又は覚醒の中枢が在るとする諸家の説と矛盾しないものである。